CHEMICALS MEETING THE CRITERIA FOR LISTING AS CAUSING CANCER VIA THE AUTHORITATIVE BODIES MECHANISM

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The chemicals listed in the table below meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The National Toxicology Program (NTP) and the U.S. Environmental Protection Agency (U.S. EPA) are two of five institutions which have been identified as authoritative bodies for the purposes of Proposition 65 (22 CCR 12306(1)). One of these bodies has identified each of the chemicals in the table below as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found these chemicals to be "formally identified" as causing cancer according to the regulations covering this issue (22 CCR 12306(d)). The chemicals below are the subject of reports published by the authoritative bodies which conclude that the chemicals cause cancer. Also, the documents specifically and accurately identify the chemicals and the documents meet one or more of the criteria outlined in 22 CCR 12306(d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (22 CCR 12306(e)) have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative bodies in making their findings that the specified chemicals cause cancer. A brief discussion of the relevant carcinogenesis studies providing evidence for the findings is presented below. The statements in bold reflect data and conclusions that satisfy the criteria for the sufficiency of evidence for carcinogenicity (22 CCR 12306(e)). The full citations for the authoritative body documents are given in this report.

Chemicals Meeting the Criteria for Listing as Causing Cancer

Chemical	CAS No.	Chemical Use	Reference
Bromate ion and its water soluble salts	-------	Chemical by-product, produced by ozonation of water containing bromide.	U.S. EPA (1998)
Bromoethane	74-96-4	Intermediate in organic synthesis, in manufacture of pharmaceuticals and in ethylation of gasoline. Also, fruit and grain fumigant[1], refrigerant and solvent.	NTP (1989a)
Isoxaflutole	141112-29-0	Experimental herbicide used for of grasses and broadleaf weeds in field corn[2].	U.S. EPA (1997)

[1] Never registered for use as a fumigant in California.
[2] Not registered for use in California.

Bromate ion and its water soluble salts

Increased incidence of malignant and combined malignant and benign tumors in male and female rats; in males, tumors were observed at multiple sites in multiple experiments.

In 1993, the U.S. EPA classified bromate as a Group B2 carcinogen (U.S. EPA, 1993). In a 1998 Health Risk Assessment, U.S. EPA (1998) stated, "Bromate should be evaluated as a likely human carcinogen by the oral route of exposure" and that the carcinogenicity of bromate in animals was demonstrated by three key sets of studies. These studies are described below.

In the first study (Kurokawa *et al.*, 1986a), male F344 rats were treated with water containing potassium bromate for 104 weeks. There were statistically significant increases in tumors at multiple sites. The combined incidences of adenoma and carcinoma of the kidney were significantly increased in animals in the two highest of six dose groups ($p < 0.001$ and $p < 0.05$ for the highest and next highest dose groups, respectively). Thyroid follicular cell adenomas and carcinomas combined were significantly increased in the high-dose group ($p < 0.05$) as were peritoneal mesotheliomas ($p < 0.05$). In the second set of studies (Kurokawa *et al.*, 1986b), bromate ion was administered in drinking water to male and female F344 rats and female $B6C3F_1$ mice. In male rats, there were statistically significant increases in renal carcinoma (3/53,24/53, and 44/52 for control, low- and high-dose groups, respectively), combined renal adenomas and carcinomas (3/53, 32/53, 46/52), and peritoneal mesotheliomas (6/53, 17/52, 28/46). In female rats, statistically significant increases in renal carcinoma (0/47, 21/50, 36/49) and renal adenomas and carcinoma combined (0/47, 28/50, 39/49) were observed. Results in mice were inconclusive.

In the third set of studies (DeAngelo *et al.*, 1998), potassium bromate was administered to male F344 rats and male B6C3F$_1$ mice in drinking water for 100 weeks. In treated male rats, statistically significant increases in renal tumors (carcinomas: 0/45, 0/43, 2/47, 1/39, 4/32; combined adenomas/carcinomas: 1/45, 1/43, 6/47, 3/39, 12/32); thyroid tumors (carcinomas: 0/36, 2/39, 0/43, 2/35, 6/30; combined adenomas/carcinomas: 0/36, 4/39, 1/43, 4/35, 14/30); and testicular mesotheliomas (0/47, 4/49, 5/49, 10/47, 27/43) were observed. Mice appeared to be less sensitive than rats to the effects of bromate exposure. In male mice, kidney tumors were observed but the incidence was not dose-dependent. U.S. EPA (1998) also noted that bromate ion has been found to be mutagenic in both *in vitro* and *in vivo* assays.

In all of the cited studies, bromate ion was administered as potassium bromate. Potassium bromate was listed as causing cancer under Proposition 65 on January 1, 1990. Potassium bromate is readily soluble in water. At drinking water pH, it (and other water soluble bromate salts) should exist almost exclusively in the ionic form. Thus, U.S. EPA (1993 and 1998) refers to dose of bromate in its documents and characterizes the potential for carcinogenicity following bromate ion exposure.

Bromoethane (CAS No. 74-96-4)

Increased incidence of malignant and combined malignant and benign tumors in female mice to an unusual degree with regard to site and incidence.

NTP (1989a) has concluded that there is clear evidence of the carcinogenic activity of bromoethane in female mice.

NTP (1989a) exposed F344/N rats and B6C3F$_1$ mice of both sexes to bromoethane via inhalation for two years. In female mice, a dose-dependent increase in endometrial uterine adenocarcinoma (0/50, 2/50, 3/47, and 19/48 for control, low-, mid- and high-dose groups, respectively) was observed in bromoethane-exposed animals. Squamous cell carcinoma of the uterus was also observed (0/50, 1/50, 1/47, 3/48). The combined incidence of adenoma, adenocarcinoma or squamous cell carcinoma of the uterus was 0/50, 4/50, 5/47, and 27/48. NTP reported the historical incidence of adenoma or adenocarcinoma of the uterus in the study laboratory as follows: nonchamber controls, 5/2,011; chamber controls, 4/335. For squamous cell neoplasms of the uterus, the historical control incidence was reported as 0/335 in chamber controls and 1/2,011 in controls from noninhalation studies.

In male mice, the incidence of alveolar/bronchiolar tumors was significantly increased in the high-dose group. However, the incidence was within the range of historical controls and there was no evidence of an increased incidence of hyperplasia in support of the finding of neoplasia. NTP concluded there was equivocal evidence for the carcinogenic activity of male B6C3F$_1$ mice.

NTP also concluded there was some evidence for the carcinogenic activity in male rats based on a significant increase in the incidence of adrenal pheochromocytomas (8/40, 23/45, 18/46, 21/46). No treatment related tumors were observed in female rats.

The NTP noted that in a separate study, inhalation of the structurally related compound chloroethane also resulted in an increased incidence of uterine carcinomas (0/49 for control and 43/50 for chloroethane-treated animals) in female $B6C3F_1$ mice (NTP, 1989b). Although the incidence of malignant tumors and the number of metastasizing tumors was lower in the bromoethane-treated mice compared to the chloroethane treated mice, the doses used in the bromoethane studies were markedly lower (100, 200 or 400 ppm in the bromoethane studies compared to15,000 ppm in the chloroethane studies). Chloroethane was listed as causing cancer under Proposition 65 in 1990 via the authoritative bodies mechanism on the basis of the NTP report. In 1991 and once again in 1999, IARC evaluated bromoethane and chloroethane and based on IARC's criteria, concluded that there was limited evidence of carcinogenicity in experimental animals in each case.

Isoxaflutole (CAS No. 141112-29-0)

Increased incidence of malignant and combined malignant and benign liver tumors in mice and rats of both sexes with early onset of tumors in male mice. There was also an increased incidence of malignant and combined malignant and benign thyroid tumors in male rats.

U.S. EPA (1997) concluded that isoxaflutole is "likely to be a human carcinogen" by all routes of exposure. This conclusion was based on statistically significant increases in liver tumors in both sexes of mice and rats with an early onset in male mice. There were also statistically significant increases in thyroid tumors in male rats. The studies considered by U.S. EPA (1997) are discussed below.

Male and female mice were exposed to isoxaflutole via diet for 78 weeks. A small group of animals was sacrificed at 53 weeks. At the 53-week interim sacrifice, the incidence of hepatocellular adenomas in high-dose male mice (7/12) was significantly greater than that in control mice (2/12), providing evidence of early onset of adenomas. In addition, the first liver carcinoma in treated male mice was observed at week 47. At 78 weeks, statistically significant increases in hepatocellular adenomas, carcinomas, and adenomas or carcinomas combined were observed in both male and female mice. Excluding the 53-week interim sacrifice animals, the incidence of hepatocellular carcinoma in male mice was 4/47, 5/50, 8/48, and 17/49 (for control, low-, mid- and high-dose groups, respectively) and in female mice, 0/51, 0/50, 0/48, and 4/51. The combined incidence of hepatocellular adenoma or carcinoma in male mice was 13/47, 15/50, 14/48, and 38/49; the incidence in female mice was 0/51, 1/50, 1/48, and 18/51.

In the rat carcinogenicity studies, male and female Sprague-Dawley rats were exposed to isoxaflutole via diet for 104 weeks. Statistically significant increases in hepatocellular adenomas and carcinomas were observed in both male and female rats. The incidence of carcinoma was 5/58, 1/53, 4/62, 2/64, and 17/68 in male rats and 0/70, 0/71, 1/69, 0/66, and 24/73 in female rats. The combined incidence of hepatocellular adenoma or carcinoma was 7/58, 4/53, 8/62, 8/64, and 31/68 for male rats and 4/70, 2/71, 2/69, 0/66, and 46/73 for female rats. The incidence of thyroid tumors was also increased in male rats. The incidences of thyroid follicular cell adenomas and carcinomas combined were significantly greater in high-dose rats than in control rats (combined adenomas or carcinomas: 3/66, 2/60, 7/69, 8/68, 17/69).

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